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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,622	12/10/2004	Joan Roig Amores	MGH-006.1P US	2699

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EXAMINER	
REDDIG, PETER J	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,622	ROIG AMORES ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *4, 7, 9, 10 and 17-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed October 4, 2007 in response to the Office Action of May 8, 2007 is acknowledged and has been entered. Previously claims 1, 3, and 8 have been amended

2. Claims 1-3, 8, and 11-16, as drawn to a non-activated Nercc1 kinase, non-activated Nek7 kinase or fusion protein thereof, detecting with an antibody, phosphorylated Nek7 kinase or fusion protein thereof, and microtiter plate for species of vessel are currently under consideration.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-3, 8, and 11-16 remain rejected under 35 U.S.C. 112, second paragraph for the reasons set forth in section 8, page 6 of the Office Action of May 8, 2007.

Applicants argue that their invention is based on the discovery that Nercc1 kinase-mediated phosphorylation of Nek6 or its homolog Nek7 is a critical step in a cascade of kinases that regulates eukaryotic cell entry into and maintenance of mitosis. See, e.g., page 4, lines 16-27; page 23, lines 19-21; Examples 10-13, pages 53-69; of the specification. According to the invention, since Nercc1 kinase-mediated phosphorylation is a critical activity in regulating mitosis, any lowering of the level of phosphorylation produced by Nercc1 kinase in the presence of an inhibitory compound compared to the level produced in the absence of the compound is sufficient to identify the compound as an inhibitor of mitosis. The Examiner is correct that the

term "a lower level" is a relative term, but the Examiner is incorrect that the term is not defined in Claim 1. Claim 1 clearly and specifically states:

> "wherein a lower level of phosphorylated kinase substrate produced in the presence of said test compound compared to the level produced in the absence of said test compound indicates that said test compound is an inhibitor of mitosis." (emphasis added).

Applicants argue that there is nothing improper or indefinite with the grammar of the above-quoted section of Claim 1. A person skilled in the art would understand that the context of the above-quoted portion of Claim 1 makes clear that the term "a lower level" with respect to the phosphorylated kinase substrate produced in the presence of the test compound is "lower" when "compared to" the level produced in the absence of the test compound and that only when there is such a comparatively (or relatively) lower level of phosphorylated substrate produced is the test compound identified as an inhibitor of mitosis. Thus, "a lower level" is indeed a relative term, and the relationship between levels of phosphorylated kinase substrate are clearly and definitively recited within Claim 1.

Applicants' arguments have been considered but have not been found persuasive because the rejection was not based on the grammatical correctness or the clarity of the relationship between levels of phosphorylated kinase substrate, but on the relative terminology in the phrase "a lower level", which is indeed a relative term, as Applicants have stated.

Applicants argue that if the grammar of Claim 1 is not in issue, the Examiner is trying to read into Applicants' claimed invention a requirement for a quantitative step that simply is not required to practice the invention, i.e., there is no requirement that a compound exceed a quantitative threshold of potency in order to be identified as an inhibitor of mitosis using

Applicants' method. The skilled practitioner is fully capable of determining whether the level of Nercc 1-mediated phosphorylation is relatively lower (or not) in the presence than in the absence of a compound as clearly stated in Claim 1. It is then up to the skilled practitioner to decide whether to develop further a compound so identified as an inhibitor of mitosis according to Applicants' claimed method. As there is no requirement under any statute that Applicants' claimed method identify only potent compounds that exhibit inhibitory properties, the use of a relative lowering of activity in the presence and absence of a test compound to practice the invention is understandable to a person skilled in the art in accordance with 35 U.S.C. 112, second paragraph. Separating strong inhibitors from weak inhibitors after the method of the invention is practiced may be a worthwhile pursuit, but it is not a critical step in the present invention, which is effective to identify the totality of inhibitors, both weak and strong.

Applicants' arguments have been considered but have not been found persuasive because although the skilled practitioner is fully capable of determining whether the level of Nercc 1-mediated phosphorylation is relatively lower (or not) in the presence than in the absence of a compound, there is no standard taught in the specification as to when the lower level of phosphorylation of Nek 7 will identify an inhibitor of mitosis, potent or weak. Indeed the specification does not teach any level of reduction of Nek7 phosphorylation mediated by Nercc1 that is indicative of inhibition of mitosis.

Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 1-3, 8, and 11-16 remain rejected under 35 U.S.C. 112, first paragraph for the reasons set forth in section 11, pages 7-13 of the Office Action of May 8, 2007.

Applicants argue that they have discovered that the Nercc1 kinase is a critical serine/threonine kinase in a cascade of kinases that regulates eukaryotic cell entry into and maintenance in mitosis. See, e.g., page 4, lines 16-27; page 23, lines 19-21; Examples 11-13, pages 55-69; of the specification. Applicants argue that they discovery that Nercc1 kinase plays a role in mitosis *is* the critical and only nexus that was necessary for Applicants to invent their claimed method wherein a compound that inhibits Nercc1 kinase activity in an *in vitro* assay is identified as an inhibitor of mitosis. Moreover, persons skilled in the art who have the benefit of having read the specification understand this role and further that a Nercc1 kinase protein is a serine/threonine kinase that has one kinase catalytic domain (see, e.g., Figure 1) and only one kinase activity, i.e., the enzymatic transfer of a phosphate group from a nucleoside triphosphate to a phosphate acceptor polypeptide molecule (kinase substrate). See, e.g., page 6, lines 14-30 and page 27, lines 16-22, of the specification. In addition, the phosphorylation of any polypeptide by a serine/threonine kinase is readily detected by methods well known in the art for assaying kinase reactions. Such methods include those mentioned in the specification such as the use of antibodies in immunodetection methods, e.g., immunnoprecipitation and/or immunoblotting methods, to detect the phosphorylated form of a kinase substrate (see, e.g., Example 7, page 48, line 24 - page 49, line 6, and Figure 4, which demonstrate use of a phospho-specific polyclonal antibody to phosphorylated Nek7), phosphoaminoacid analysis to detect

phosphorylated amino acid residues, such as serine or threonine of a phosphorylated kinase substrate (see, e.g., page 46, lines 23 - 25, of the specification), and direct radiodetection of a radiolabeled kinase substrate molecule that has accepted a radiolabeled phosphate from a radiolabeled nucleoside triphosphate donor molecule (see, e.g., page 7, line 23 - page 8, line 5 and page 46, lines 25 - 27, of the specification). See, also, the classic description of versatile protein kinase assays by Roskoski, Jr., R., "Assays of Protein Kinase," *In* Methods In Enzymology, Vol. 99, Hormone Action, Part F, Protein Kinases, (Corbin and Hardman, eds.) (Academic Press, New York, 1983) pages 3-6; attached at Tab A.

Applicants' arguments have been considered, but have not been found persuasive because although Nercc1 is a kinase involved in mitosis and kinase assays are well known in the art, Applicants have not established a nexus between Nercc1, phosphorylation of the specific Nek7 substrate, and the inhibition of mitosis for the reasons previously set forth.

Applicants argue that the Nercc1 kinase is a serine/threonine kinase. See, e.g., page 46, lines 23-25 in Example 6, of the specification. A variety of polypeptides are known to persons skilled in the art that may be used as substrates in *in vitro* assays for such kinases. See, e.g., page 6, lines 16-30, of the specification. Furthermore, Applicants' specification provides results that illustrate that an *in vitro* assay for Nercc1 kinase activity may not only employ a physiological substrate, such as Nek6 or Nek7 (see, e.g., page 48, line 26-page 49, line 6 in Example 7 and page 66, lines 15-17 in Example 12, of the specification), but also such well known *in vitro* kinase substrates as histones (e.g., histone H3), myelin basic protein (MBP), and casein. See, e.g., page 46, lines 21-25 in Example 6 and page 66, lines 20-24 in Example 12, of the specification.

Applicants' arguments have been considered, but have not been found persuasive because although Nercc1 is a kinase that phosphorylates Nek 7 in vitro, kinase assays, and kinase substrates are well known in the art, Applicants have not established a nexus between Nercc1, phosphorylation of the specific Nek7 substrate, and the inhibition of mitosis for the reasons previously set forth.

Applicants argue that the metabolic "function" or "role" of a phosphorylated reaction product of an *in vitro* Nercc1 kinase assay is irrelevant to the practice of the claimed method, because the method is based on detecting whether or not a compound can inhibit Nercc 1 mediated-phosphate transfer *in vitro* to an acceptor molecule, not whether the resulting phosphorylated reaction product, itself, also plays a role in mitosis. The function, if any, of the phosphorylated substrate is irrelevant to Applicants' invention, since the object is accomplished by the fact of phosphorylation (not whether the phosphorylation or inhibition thereof has a medical use). Applicants' claimed method employs an *in vitro* assay to detect inhibition .of the Nercc1 kinase activity, which Applicants have shown plays a critical role in the regulation of mitotic progression. Accordingly, persons skilled in the art who read Applicants' specification would understand that there is no reason to prove that there is a nexus between the phosphorylated kinase substrate of the assay and mitosis (even if one exists as in the case of Nek6 or Nek7) in order to understand and practice Applicants' claimed invention. Description so as to enable practice of the invention is the requirement of 35 U.S.C. 112, first paragraph.

Applicants' arguments have been considered, but have not been found persuasive because the art teaches that phosphorylation of different substrates by Nercc1 does not predictably indicate a Nercc1 mediated effect on mitosis, thus in the absence of empirical evidence of a

nexus between Nercc1, Nek7 phosphorylation, and mitosis the claimed method is not enabled. Although, one of skill in the art may be able to perform the claimed method, one could not predictably use the method as contemplated by the specification and claimed to identify a compound that is an inhibitor of mitosis without undue experimentation.

Applicants argue that at page 9 of the Office Action, the Examiner stated:

"Thus, in view of the above, the claims read on identifying compounds for identifying inhibitors of mitosis that will treat cancer and/or eukaryotic microbial infections."

Applicants argue that the above-quoted excerpt from the Office Action indicates that the Examiner is attributing an efficacy to products of the method of the invention that simply is not stated in any of Claims 1-3, 8, and 11-16. Applicants have discovered and claim a reliable way of testing compounds for the ability to inhibit mitosis based on their ability to inhibit *in vitro* the kinase activity of a Nercc1 kinase protein. Nercc1 kinase is shown by Applicants to play a critical role in a cascade of kinases that signals eukaryotic cells to enter and/or continue in mitosis. Some inhibitors of mitosis may indeed be candidates for treating cancer or eukaryotic microbial infection, as both types of diseases involve undesired mitotic progression, but such anti-cancer or anti-microbial activities are not required elements of the invention and properly are not required elements in any of the claims under examination. Applicants note in passing that compounds that inhibit mitosis have been and continue to be a well known source of potential anti-cancer agents. See, e.g., the review by Jackson et al., *Nature Reviews Cancer, 7:107-117* (2007) attached at Tab B. Perhaps the best known example of an inhibitor of mitosis that has been developed as an anti-cancer agent is paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, New Jersey). See, paclitaxel patient information sheets attached at Tab C. Nevertheless, such potential utilities are

not part of Applicants' claimed invention for identifying an inhibitor of mitosis. Indeed, Applicants' disclosure specifically teaches that compounds identified as inhibitors of mitosis may be further investigated for one or more therapeutic activities:

> "Compounds initially identified as inhibitors of mitosis (i.e., anti-mitotic compounds) according to the method described above may be further characterized for the ability to inhibit or halt mitosis in proliferating (actively dividing) cells, either *in vitro* or *in vivo*. The cells employed in this further characterization step may be any of a variety of proliferating cells, including but not limited to, non-cancerous cells, cancer cells, or cells of a eukaryotic pathogen of interest. Preferably, the proliferating cells are cancer cells or cells of a eukaryotic pathogen of interest. (page 29, lines 11-17, of the specification; underlining added for emphasis).

Accordingly, Applicants clearly recognized that a compound that is identified as an inhibitor of mitosis based on its ability to inhibit Nercc1 kinase activity in an *in vitro* assay may also provide one or more therapeutic activities. However, the effectiveness of any compound identified as an inhibitor of mitosis according to Applicants' claimed method in treating cancer or a eukaryotic microbial infection is simply not an object or required element of the claimed invention. Confirmation of such therapeutic benefits requires carrying out further steps to characterize the inhibitor compound (see, e.g., withdrawn Claims 17-19), but such additional steps are not a critical feature of the claimed invention.

Applicants' arguments have been considered, but have not been found persuasive because the claims are drawn to identification of a compound that is an inhibitor of mitosis with the contemplated uses of treating cancer or eukaryotic microbial infection and given that the art

teaches that phosphorylation of different substrates by Nercc1 does not predictably indicate a Nercc1 mediated effect on mitosis in the absence of empirical evidence of a nexus between Nercc1, Nek7 phosphorylation and mitosis, the claimed method is not enabled. Although, an inhibitor of mitosis would predictably be useful to one of skill in the art, the claimed method does not predictably allow for the identification of said inhibitor without undue experimentation.

6. All other objections and rejections recited in the Office action of May 8, 2007 are withdrawn.

7. No claims allowed.

8. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection

unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of 1.136(a) time policy as set forth in 37 C.F.R.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OFPURSUANT TO 37 C.F.R. THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Peter J. Reddig
Examiner
Art Unit 1642

PJR